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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/659,983	09/12/2000	Robert Hans Meloen	4518US	6015

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/659,983	MELOEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10-12,15,20,21,26-28,34-36,51 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-12,15,20,21,26-28,34-36,51 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 12 September 2000 (Paper No. 6 and Paper No. 7) have been entered in full. Claims 26-54 were added. The amendment filed 16 January 2001 (Paper No. 8) has been entered in full. The amendment filed 21 May 2001 (Paper No. 13) has been entered in full. The amendment filed 27 August 2001 (Paper No. 20) has been entered in full.

The amendment filed 15 May 2002 (Paper No. 27) has been entered in full. Applicant's election of Group I (claims 1-5, 10-12, 15, 20, 21, 26-28, 34-36, 51 and 52) in Paper No. 27 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 6-9, 13, 14, 16-19, 22-25, 29-33, 37-50, 53 and 54 have been cancelled. Claims 1-5, 10-12, 15, 20, 21, 26-28, 34-36, 51 and 52 are under examination.

Specification

The specification is objected to because this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

In Figure 4, (page 13, line 16), it should read, "all 4 pigs were immunocastrated" not "all 2 pigs were immunocastrated".

Claim Rej ctions - 35 USC § 112

Claims 20, 21, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 20 and 51 are generally drawn to a vaccine against GnRH-II comprising the peptide of claim 1 and claim 5 respectively. Claims 21 and 52 are generally drawn to a composition for the treatment of prostate cancer comprising the peptide of claim 1 and claim 5 respectively. The instant specification states that the presence of GnRH-II in diverse tissues other than the brain suggests that GnRH-II may have multiple functions and that it seems less involved in reproduction as compared to GnRH-I (page 4, lines 5-8 and 14). The specification states that nothing is known about any physiological effects of the antibodies raised against GnRH-II on the function of GnRH-II. Antibodies raised against GnRH-I that cross-react with GnRH-II may affect kidney function. It would be desirable to direct the antigenic response of immunocastration vaccine specifically toward GnRH-I and to avoid possible harmful side effects due to neutralization of non-gonadal GnRH-II (page 5, lines 1-7). The specification states that in human health care, immunization against GnRH-I and/or GnRH-II can be used in the treatment of prostate cancer and, if required, the treatment of some forms of pituitary carcinoma. In the case of prostate cancer it might be more desirable to neutralize both GnRH-I and GnRH-II, as the later isoform is also highly expressed in prostate tissue (page 5, lines 20-24).

The specification is not enabled for the instant claims because the specification has not taught to how to make a vaccine against GnRH-II. The specification states that peptides according to the invention express an increased or retained activity against GnRH-I, while at the same time a reduced or absent immune response to GnRH-II (page 11, lines 3-9). Secondly, the specification states that the physiological effects of antibodies raised against GnRH-II on the function of GnRH-II are unknown. The specification states that antibodies that cross react with GnRH-II could have side effects against kidney function since GnRH-II is mainly synthesized in the kidneys. Lastly, the specification states that immunization against GnRH-II (a GnRH-II vaccine) *could* be used in prostate cancer in humans. This treatment, however, is hypothetical and the specification has not disclosed examples demonstrating that a GnRH-II vaccine could specifically target prostate cancer and not have a deleterious effect on other functions in the body. Therefore in view of the dubious nature of GnRH-II vaccines, claims 20, 21, 51 and 52 are not enabled.

Due to the large quantity of experimentation necessary to construct a GnRH-II vaccine that would specifically target prostate cancer and not have a deleterious effect on other functions in the body, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the contradictory state of the prior art regarding GnRH-II, and the unpredictability of the effects of a GnRH-II vaccine on other biological functions in the body, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 4 and 26 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide comprising at least two coupled GnRH decapeptide sequence capable of inducing an immunogenic response that allows for discrimination between different types of GnRH wherein the peptide sequence is SEQ ID NO:5. SEQ ID NO:6 or SEQ ID NO:7, does not reasonably provide enablement for the claims as cited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

The specification is not enabled because it fails to show that a peptide comprising *any modified* tandem GnRH decapeptide coupled sequence is capable of inducing an immunogenic response that allows for discrimination between different types of GnRH, wherein at least one of the amino acids of said coupled GnRH decapeptide sequences is replaced by Ala. The instant specification teaches exact alanine substitutions in specific GnRH decapeptides coupled sequences capable of inducing responses, which also allow for discrimination between GnRH-I and GnRH-II (SEQ ID NO:5. SEQ ID NO:6 and SEQ ID NO:7). It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified polypeptide could be used in the same manner as the native exemplar.

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity (see Daniel *et al.* 1994, Virology 202:540-549). These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.*, 1994). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to modifications and the nature and extent of changes that can be made in these positions that would still enable the protein to induce an immunogenic response and allows for discrimination between different types of GnRH.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "said different amino acid". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 1,2,3,10-12,15, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alston-Mill *et al.* In Vitro Cell. Dev. Biol. in view of Dufour *et al.* U.S. Patent No. 5,573,767 A.

Alston-Mill teaches the *in vivo* and *in vitro* immunization protocol to generate monoclonal antibodies against the decapeptide luteinizing hormone-releasing hormone (LHRH) also known as GnRH. LHRH-I was injected into mice (abstract, page 935 immunization protocol). The antibody cross-reacted with LHRH-I and II but preferentially to LHRH-I as shown by competitive assay (see abstract, Figure 3 and page 938 last paragraph). Alson-Mills does not teach tandem decapeptides, modification of the decapeptide, immunocastration vaccines, or adjuvants.

Dufour states that it is possible to seek to abolish or decrease the secretion of testicular steroids by immunoneutralization of the gonadotropic hormone LH specific to

the species in question (column 1, line 65-column 2, line 7). Dufour teaches the advantages of using immunoneutralization over castration (column 2, lines 14-42). Dufour cites a method of anti-LHRH immunization at birth, using 2 LHRH sequences in tandem coupled to a carrier protein to improve meat quality in pigs (column 2, lines 34-37). Dufour teaches the modification of the LHRH peptide wherein at least one of the amino acids of the decapeptide is replaced by a different amino acid (column 4, line 48-column 5, line 6). Dufour teaches that the anti-LHRH vaccine is administered in emulsion form (column 3, lines 18-21). For pigs, it is especially advantageous to administer, before slaughter, the anti-LHRH vaccine with an aqueous type adjuvant (column 3, lines 25-28). In pigs, the conjugate in aqueous solution is put into two formulations, one being in the form of a stable water-in-oil emulsion (column 3, lines 51-62). Dufour teaches a vaccine which is active for administration in a single dose for the immunocastration of pigs. Dufour states hyperimmune anti-LHRH serum or plasma or alternatively LHRH monoclonal antibodies are administered to the animal a few days before slaughter, in particular 5 to 15 days before hand. The immunization brings about a decrease in plasma testosterone from day 3 onwards (column 4, lines 9-25 and Table 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Alston-Mill regarding the production of antibodies using the teachings of Dufour regarding modification of tandem decapeptides, immunocastration vaccines and adjuvants. The motivation and expected success is provided by Alston-Mills who teaches that GnRH peptides can induce an

immunogenic response thus producing antibodies which can differentiate between different types of GnRH and Dufour who teaches that vaccines made against GnRH can successfully immunocastrate various animals by neutralizing endogenous GnRH.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
July 29, 2002

GARY L. KUNZ
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